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## In This Issue



# Amprenavir (Agenerase™): A Brief Review

Amprenavir (Agenerase™, Glaxo Wellcome) is an HIV-1 protease inhibitor which received accelerated approval by the FDA in April of 1999. It is the fifth protease inhibitor to become available in the United States.

### *Dosage Forms / Formulation*

Amprenavir (APV) is available in 50-mg and 150-mg oblong off-white to cream colored soft gelatin capsules. It is also available in a 15-mg/mL oral solution with a grape bubblegum peppermint flavor. The capsules and oral solution are not interchangeable on a milligram to milligram basis.

Amprenavir capsules contain 109 IU of vitamin E (total daily dose 1744 IU) and the solution contains 46 IU of vitamin E per mL. Therefore, patients receiving this medication should not take supplemental vitamin E since it will exceed the recommended daily intake of 30 IU.

### *Indications*

Amprenavir is approved for use in both adults and children (studies were performed in patients 4 years of age or older). It is indicated in combination with other antiretroviral agents for the treatment of HIV infection. The approval was based on HIV RNA and CD4 data from controlled studies of up to 24 weeks in duration. No data evaluating long term viral suppression or clinical endpoints are available.

### *Mechanism of Action*

HIV protease is a critical enzyme in the latter stage of the replication cycle. Amprenavir binds to the active site of HIV protease preventing the cleavage of viral polyprotein precursors. This results in the formation of immature, non-infectious viral particles thus breaking the cycle of replication. The inhibitory concentration of amprenavir ranges from 0.012 to 0.08 μM in acutely infected cells and 0.41 μM in cells infected chronically. In vitro, amprenavir has exhibited synergistic activity with abacavir (ABC), zidovudine (AZT), didanosine (DDI), and saquinavir (D4T). It has also shown to have an additive activity when administered with indinavir, nelfinavir and ritonavir.

### *Resistance*

HIV-1 isolates with reduced susceptibility to amprenavir have been selected in vitro and obtained from patients treated with amprenavir. Amprenavir-treated patients have demonstrated genotypic mutations in the HIV protease gene with substitutions at M46I/L, I47V, I50V, I54L/V, and I84V. Mutations at codons 10, 54, and 84 foster cross-resistance to other protease inhibitors. Phenotypic analysis of patients treated with monotherapy or combination therapy with amprenavir has demonstrated a five to eleven fold decrease in susceptibility compared to wild-type virus after 8-36 weeks of therapy.

### *Pharmacokinetics*

Amprenavir is rapidly absorbed following oral administration and reaches its peak serum concentration within one to two hours. The absolute bioavailability is estimated to be 89% based on animal data. The oral solution is 14% less bioavailable compared to the capsules. Administration with a high fat meal (67 grams of fat) resulted in a decrease in the AUC of approximately 21%. Amprenavir may be taken with or without food but should not be taken with a high fat meal. This agent has a large volume of distribution

of 430 L and is 90% plasma protein bound. It is primarily metabolized in the liver (via the CYP3A4 isoenzyme) to two major inactive metabolites. The drug's elimination half-life ranges between 7.1-10.6 hours. Approximately 75% of a single dose is recovered in the stool and 14% in the urine. The pharmacokinetics of this agent do not appear to be affected by patients' gender or racial background. Amprenavir's pharmacokinetic parameters have not been evaluated in adults over 65 years of age.

### *Pivotal Clinical Studies*

*PROAB3001.* This was a Phase III, double-blinded international study that compared a regimen of APV, AZT, and 3TC to AZT plus 3TC in 232 treatment naive patients with a baseline viral load > 10,000 copies/mL and CD4 cell count > 200 cells/mm3. By intent to treat analysis at 16 weeks, the percentage of patients with viral loads < 400 copies/ml was 79% in the three drug arm vs. 19% in the two drug arm. According to the as-treated comparison, the percentage of patients with a viral load of < 50 copies/mL was 80% and 18% in the triple and double combination groups, respectively. CD4 cell counts were increased in both groups. Adverse events were similar between groups but nausea, rash, and oral parasthesias were more common in the APV + AZT + 3TC arm.

*PROAM3006.* This was a randomized, ongoing open label study comparing APV or indinavir with two nucleoside reverse transcriptase inhibitors (NRTI) in 504 patients with prior NRTI or nonnucleoside reverse transcriptase inhibitor (NNRTI) experience. Baseline median CD4 cell count was 399 cells/mm3 and the baseline viral load was 3.93 log. Intention to treat analysis at 24 weeks showed a viral load of < 400 copies/mL in 43% of patients treated with APV and 53% of patients in the indinavir group. In addition, the CD4 cell count was found to be higher in the indinavir-treated group.

*ACTG 347.* This study compared APV monotherapy vs. APV + AZT + 3TC in 92 treatment-naive patients. The percentage of patients with a viral load of > 500 copies/mL at 12 weeks was 2% in the triple therapy arm and 28% in those receiving APV monotherapy.

*PRO2007.* This study examined a regimen of APV, efavirenz, and abacavir in 99 patients who had a viral load of > 500 copies/mL despite 20 weeks of therapy with a protease inhibitor. Patients were stratified by viral load (> or < 40,000) and NNRTI experience. At week 16, the percentage of patients with a viral load of < 400 copies/mL ranged from 7% in patients with high baseline viral load and NNRTI experienced to 53% in low viral load and NNRTI naive. The CD4 increases were also greatest in the latter group with a median increase of approximately 60 cells/mm3.

*PROOAB 3004.* This was a randomized, double-blind, placebo controlled study which included 81 children (ages 4-17 years old). The study was later amended to an open label design in which all patients received amprenavir. Subjects included both protease inhibitor-experienced or naive children who were randomized to receive APV oral solution at a dose of 20 mg/kg BID (1.5 mL/kg BID) with two NRTIs. Baseline viral load ranged from 3.0 to 5.8 log copies/mL and the median CD4 count was 474 cells/mm3. At 8 weeks, the overall percentage of patients with a viral load of < 400 copies/mL was 41% which later decreased to 22% by week 12. The response was significantly higher (58%) in protease naive subjects. At week 8, the median increase in CD4 cell count was 20 and 15 in the protease naive and experienced groups, respectively. Amprenavir was generally well tolerated and adverse effects were primarily gastrointestinal in nature.

Bart and colleagues examined APV + abacavir (ABC) in 41 treatment-naive patients with baseline viral load > 5000 and baseline CD4 cell count of > 400 cells/mm3. Intent-to-treat analysis and as-treated analysis at 60 weeks showed the percent of patients with a viral load of < 50 and < 500 copies/mL to be 58% and 78%, respectively. This was accompanied by a mean CD4 increase of 265 cells (130 naive, 84 memory). An increase in serum cholesterol concentrations was observed during the study but changes in serum glucose and triglyceride concentrations were not statistically different from baseline.

### *Adverse Effects*

Safety data have been accumulated on 1329 adults and 148 pediatric patients receiving amprenavir. The most common adverse effects in clinical trials with combination therapy were gastrointestinal (nausea, vomiting, diarrhea) in up to 70% of patients. A maculopapular rash is observed in up to 25% of patients, and usually occurs at 1-3 weeks of therapy. With mild to moderate rashes, dosing can be continued. If discontinued, reintroduction often proceeds without re-development of the rash. A few cases of Stevens Johnson syndrome have also been reported. In clinical studies, adverse events leading to discontinuation of therapy included gastrointestinal events (11%), rash (3%), and oral parasthesias (<1%). Increases in liver function tests and amylase serum concentrations, and decrease in neutrophil counts have been reported in 5% or less of patients.

There have been four reports of fat redistribution with amprenavir in clinical trials. One case of a buffalo hump was reported in a protease inhibitor-naive patient on study day 99 of amprenavir + D4T + 3TC. Additionally, three other patients who were heavily pretreated with protease inhibitors experienced fat redistribution symptoms. Two had symptoms occur less than two months into amprenavir treatment, and one had recurrence of the buffalo hump on study day 103.

### *Drug Interactions*

Amprenavir is an inhibitor of the CYP3A4 isoenzyme (comparable potency to indinavir and nelfinavir). Therefore, it carries the same interaction precautions as the other

protease inhibitors. The use of astemizole, bepridil, cisapride, dihydroergotamine, ergotamine, midazolam, terfenadine, triazolam, and rifampin is contraindicated in patients receiving amprenavir. Serun concentration monitoring may be required with amiodarone, lidocaine, quinidine, tricyclic antidepressants, and warfarin when they are used in combination with amprenavir. In addition, the dose of rifabutin must be decreased by half when it is used concomitantly with amprenavir. Other clinically significant interactions include those with HMG-CoA reductase inhibitors, phenobarbital, phenytoin, carbamazepine, sildenafil, and oral contraceptives (use alternative method).

Much of the drug interaction data reported in the package insert should be viewed with caution since the data involves small numbers of patients and many of the analysis are either between separate groups of patients or with historical controls.

### *Dosing (in combination with other antiretrovirals)*

*Adults:*

Amprenavir is administered as an oral dose of 1200 mg (eight 150 mg capsules) twice daily and may be given with or without food.

*Pediatrics (capsules):*

13-16 years: 1200 mg (eight 150 mg capsules) twice daily.

4-12 years or patient 13-16 years but less than 50 kg: 20 mg/kg twice daily or 15 mg/kg three times daily up to a maximum of 2400 mg/day

*Pediatrics (oral solution):*

4-12 years or patient 13-16 years less than 50 kg: 22.5 mg/kg twice daily or 17 mg/kg three times daily up to a maximum of 2800 mg/day

*Special population:*

Amprenavir should be used with caution in patients with moderate to severe hepatic impairment. Patients with a child Pugh score ranging from 5-8 and 9-12, should receive a reduced dose of 450 mg twice daily and 300 mg twice daily, respectively.

**Table 1. Cost**

| Protease Inhibitors | Monthly Cost* |
|---|---|
| Ritonavir | $369.52 |
| Indinavir | $268.41 |
| Nelfinavir | $346.72 |
| Saquinavir-SGC | $363.78 |
| Amprenavir | $375.38 |

** Federal Supply Schedule (30-day supply at standard doses)*

### *Conclusion*

Amprenavir is the fifth protease inhibitor available for use in the treatment of HIV infection. It appears to be comparable in efficacy to other drugs in its class when given as part of a combination regimen. Long-term viral suppression has yet to be determined. The adverse effect profile is characterized primarily by gastrointestinal side effects. In addition, skin rash appears to be more commonly seen with amprenavir in comparison to other protease inhibitors. This may complicate combination therapy with other drugs which share the same side effect such as NNRTIs, abacavir, and Co-trimoxazole.

Amprenavir offers the advantage of being dosed twice daily with or without food, and there are some in vitro data which suggest that fat redistribution and metabolic complications may occur less frequently with this agent. However, this will be confirmed only after the drug has been widely used. Studies examining the use of amprenavir with other protease inhibitors are ongoing. It is also being evaluated as part of a regimen for salvage therapy. Each available protease inhibitor has problematic issues regarding interactions, formulations, dosing, and resistance. Amprenavir does not eliminate any of these complicated issues but does offer clinicians another option in constructing an effective regimen.

## Did You Know ...

- Orlistat (Xenical®) has been approved for the management of obesity. Orlistat is a lipase inhibitor which inhibits the absorption of approximately 33% of dietary fat. The most common adverse events seen with this agent include oily spotting, fecal urgency, fatty stools, and fecal incontinence. The recommended dose of orlistat is 120 mg three times daily with each meal.
- The FDA has approved cytarabine liposomal injection (DepoCyt®) for the intrathecal treatment of lymphomatous meningitis. The most common adverse event associated with the use of this agent is chemical arachnoiditis (a syndrome characterized by nausea, vomiting, headache, and fever). Cytarabine liposomal injection is available as 5-mL single-dose vials, each containing 50 mg of cytarabine.
- An FDA advisory committee has recommended approval of rofecoxib (Vioxx®) for the management of osteoarthritis and acute short-term pain. The committee recommended that the labeling carry the same warnings as the NSAID class regarding the possibility of gastrointestinal side effects.
- Hextend® (6% hetastarch in balanced electrolyte solution), a new blood-plasma volume expander, was recently approved for management of hypovolemia due to blood loss during surgery.
- 17-ß-estradiol (Vagifem®), a vaginal tablet insert, has been approved for the treatment of atrophic vaginitis. Mild adverse events associated with the use of this agent include vaginal spotting or discharge, and skin rash.

# Formulary Update:

The Pharmacy and Therapeutic Committee recently approved the following formulary actions:

***Additions:***

- Cetirizine (Zyrtec®), a second generation antihistamine indicated for the management of chronic idiopathic urticaria and allergic rhinitis.
- Amprenavir (Agenerase®), an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV infection.
- Tacrolimus (Prograf®), a macrolide immunosuppressant indicated for prophylaxis of organ rejection in patients receiving allogeneic liver transplants.
- Mycophenolate mofetil (CellCept®), an immunosuppressant indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal or cardiac transplant.
- Daclizumab (Zenepax®), a humanized IgG-1 monoclonal antibody indicated for the prophylaxis of acute organ rejection in patients receiving renal transplants.
- Antithymocyte globulin-rabbit (Thymoglobulin®), indicated for the management of allograft rejection in renal transplant patients.
- Cytomegalovirus IgG (Cytogam®), used for the attenuation of primary CMV disease associated with kidney transplantation.
- Primaquine, an 8-aminoquinoline used as second-line therapy for pneumocystis carinii pneumonia
- Viaspan® (organ preservative solution)

***Editors' Note***

We wish to thank Steve Piscitelli, Pharm.D. for his contribution to this issue of *Pharmacy Update*.

## Drug Information Service

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